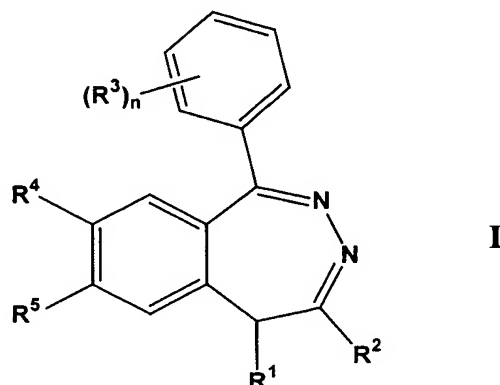


CLAIMS

What is claimed is:

1. A method of increasing the absolute neutrophil count in an individual, comprising administering to said individual an effective amount of at least one compound of formula I:



wherein:

R^1 is $-(C_1-C_7)$ hydrocarbyl or $-(C_2-C_6)$ heteroalkyl;

R^2 is selected from the group consisting of $-H$, and $-(C_1-C_7)$ hydrocarbyl;

wherein R^1 and R^2 may combine to form a carbocyclic or heterocyclic 5- or 6-membered ring;

R^3 is independently selected from the group consisting of $-O(C_1-C_6)$ alkyl, $-OH$, $-O$ -acyl, $-SH$, $-S(C_1-C_3)$ alkyl, $-NH_2$, $-NH(C_1-C_6)$ alkyl, $-N((C_1-C_6)alkyl)_2$, $-NH$ -acyl, $-NO_2$ and halogen;

n is 1, 2 or 3;

R^4 and R^5 are independently selected from the group consisting of $-O(C_1-C_6)$ alkyl, $-OH$, O -acyl, $-SH$, $-S(C_1-C_3)$ alkyl, $-NH_2$, NH -acyl and halogen;

wherein, R^4 and R^5 may combine to form a 5, 6 or 7-membered heterocyclic ring;

or a pharmaceutically-acceptable salt of such a compound.

2. The method according to claim 1 wherein the compound according to formula I comprises a racemic mixture of (*R*)- and (*S*)- enantiomers with respect to the absolute conformation at the 5-position of the benzodiazepine ring.
3. The method according to claim 1, wherein:
 - R^1 is $-(C_1-C_6)alkyl$;
 - R^2 is selected from the group consisting of $-H$ and $-(C_1-C_6)alkyl$;
 - R^3 is independently selected from the group consisting of $-O(C_1-C_6)alkyl$, $-O-acyl$ and $-OH$;
 - n is 1, 2 or 3;
 - R^4 and R^5 are independently selected from the group consisting of $-O(C_1-C_6)alkyl$, $-O-acyl$ and $-OH$, wherein, R^4 and R^5 may combine to form a 5, 6 or 7-membered heterocyclic ring;
 - or a pharmaceutically-acceptable salt of such a compound.
4. The method according to claim 3, wherein:
 - R^1 is $-CH_2CH_3$;
 - R^2 is $-CH_3$;
 - R^3 , R^4 and R^5 are independently selected from the group consisting of $-OH$ and $-O(C_1-C_6)alkyl$;
 - n is 1, 2 or 3;
 - or a pharmaceutically-acceptable salt of such a compound.
5. The method according to claim 4, wherein:
 - R^1 is $-CH_2CH_3$;
 - R^2 is $-CH_3$;
 - R^3 , R^4 and R^5 are independently selected from the group consisting of $-OH$ and $-OCH_3$;
 - n is of 1, 2 or 3;
 - or a pharmaceutically-acceptable salt of such a compound.

6. The method according to claim 5, wherein the compound is selected from the group consisting of:

1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine;

1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine;

1-(3-hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine;

1-(3-methoxy-4-hydroxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine;

1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine;

1-(3-methoxy-4-hydroxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine;

1-(3-hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine;

and pharmaceutically acceptable salts thereof.

7. The method according to claim 6, wherein the compound is 1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine; or a pharmaceutically acceptable salt thereof.

8. The method according to claim 1, wherein said compound according to formula I is an (*R*)-enantiomer substantially free of the corresponding (*S*)-enantiomer, with respect to the absolute conformation at the 5-position of the benzodiazepine ring.

9. The method according to claim 8, wherein:

R^1 is $-(C_1-C_6)alkyl$;

R^2 is selected from the group consisting of $-H$ and $-(C_1-C_6)alkyl$;

R^3 is independently selected from the group consisting of $-O(C_1-C_6)alkyl$, $-O-acyl$ and $-OH$;

n is 1, 2 or 3;

R^4 and R^5 are independently selected from the group consisting of $-O(C_1-C_6)alkyl$, $-O-acyl$ and $-OH$, wherein, R^4 and R^5 may combine to form a 5, 6 or 7-membered heterocyclic ring;

or a pharmaceutically-acceptable salt of such a compound.

10. The method according to claim 9, wherein:

R^1 is $-CH_2CH_3$;

R^2 is $-CH_3$

R^3 , R^4 and R^5 are independently selected from the group consisting of $-OH$ and $-O(C_1-C_6)alkyl$;

n is 1, 2 or 3;

or a pharmaceutically-acceptable salt of such a compound.

11. The method according to claim 10, wherein:

R^1 is $-CH_2CH_3$;

R^2 is $-CH_3$

R^3 , R^4 and R^5 are independently selected from the group consisting of $-OH$ and $-OCH_3$;

n is of 1, 2 or 3;

or a pharmaceutically-acceptable salt of such a compound.

12. The method according to claim 11, wherein the compound is selected from the group consisting of:

(*R*)-1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine;

(*R*)-1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine;

(*R*)-1-(3-hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine;

(*R*)-1-(3-methoxy-4-hydroxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine;

(*R*)-1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine;

(*R*)-1-(3-methoxy-4-hydroxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine; and

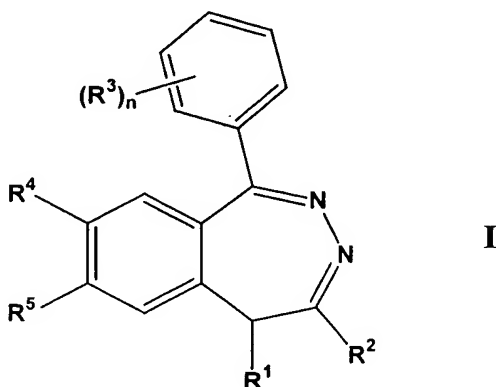
(*R*)-1-(3-hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine, substantially free of the corresponding (*S*)-enantiomers;

and pharmaceutically acceptable salts thereof.

13. The method according to claim 12, wherein the compound is (*R*)-1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine, substantially free of the corresponding (*S*)-enantiomer;

or a pharmaceutically acceptable salt thereof.

14. A method of treating an individual afflicted with neutropenia, comprising administering to said individual an effective amount of at least one compound of formula I:



wherein:

R^1 is $-(C_1-C_7)$ hydrocarbyl or $-(C_2-C_6)$ heteroalkyl;

R^2 is selected from the group consisting of $-H$, and $-(C_1-C_7)$ hydrocarbyl;

wherein R^1 and R^2 may combine to form a carbocyclic or heterocyclic 5- or 6-membered ring;

R^3 is independently selected from the group consisting of $-O(C_1-C_6)$ alkyl, $-OH$, $-O$ -acyl, $-SH$, $-S(C_1-C_3)$ alkyl, $-NH_2$, $-NH(C_1-C_6)$ alkyl, $-N((C_1-C_6)alkyl)_2$, $-NH$ -acyl, $-NO_2$ and halogen;

n is 1, 2 or 3;

R^4 and R^5 are independently selected from the group consisting of $-O(C_1-C_6)alkyl$, $-OH$, $O-acyl$, $-SH$, $-S(C_1-C_3)alkyl$, $-NH_2$, $NH-acyl$ and halogen;

wherein, R^4 and R^5 may combine to form a 5, 6 or 7-membered heterocyclic ring;

or a pharmaceutically-acceptable salt of such a compound.

15. The method according to claim 14, wherein said compound according to formula I is an (*R*)-enantiomer substantially free of the corresponding (*S*)-enantiomer, with respect to the absolute conformation at the 5-position of the benzodiazepine ring.

16. The method according to claim 15, wherein the neutropenia treated is a side effect of drug therapy.

17. The method according to claim 16 wherein the drug therapy comprises administration of at least one chemotherapeutic agent.

18. The method according to claim 16 wherein the drug therapy comprises administration of at least one therapy selected from the group consisting of thyroid inhibitors, antibiotics, neuropsychotropics, cardiovascular medications, analgesics, antimalarials, nonsteroidal antiinflammatory agents, antihistamines and combinations thereof.

19. The method according to claim 18 wherein the drug therapy comprises administration of at least one drug selected from the group consisting of trimethoprim, chloramphenicol, penicillins, cephalosporins, aminoglycosides, tetracyclines, nitroimidazoles, nitrofurantoin, flucytosine, rifampin, isoniazid, ethambutol, dapsone, sulfonamide antibiotics, clomiprimine, thiacetazone, dipyrone, sulfasalazine, mesalazine, ciprofloxacin, chloroquin, mebendazole, terbendafine, pyrimethamine, levamisole, ristocetin, griseofulvin.

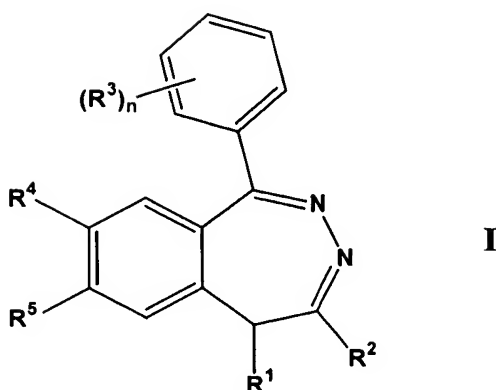
phenothiazines, benzodiazepines, amoxapine, meprobamate, barbiturates, clozapine, risperidone, imipramine, desipramine, thiothixene, haloperidol, valproic acid, hydantoins, succinimides, trimethadione, carbamazepine, procainamide, quinidine, propafenone, captopril, propranolol, hydralazine, methyl dopa, ibuprofen, indomethacin, sulindac, tolmetin, aspirin, aminopyrine, phenylbutazone, diflunisal, benoxaprofen, allopurinol, colchicine, propylthiouracil, thiouracil, methimazole, carbimazole, thiocyanate, potassium perchlorate, cimetidine, ranatadine, tripeleennamine, methaphenilene, thenalidine, mianserin, bromopheneramine, quinine, hydroxychloroquin, quinacrine, diazoxide, dihydropyridines, ticlopidine, vesnarinone, aprindine, imipenem/cilastatin, zidovudine, fludarabine, acyclovir, turbinafine, aminoglutethimide, famotidine, bezafibrate, flutamide, tamoxafen, penicillamine, retinoic acid, metoclopramide, phenindone, dinitrophenol, ethacrynic acid, rauwolfia, ethanol, chlorpropamide, tolbutamide, thiazides, spironolactone, methazolamide, acetazolamide, levodopa and combinations thereof.

20. The method according to claim 15, wherein the neutropenia treated is a side effect of exposure of an individual to ionizing radiation.

21. The method according to claim 20 wherein the ionizing radiation comprises therapeutic radiation therapy.

22. The method according to claim 20 wherein the ionizing radiation is other than therapeutic radiation therapy.

23. A method of preventing neutropenia in an individual who is at risk of developing neutropenia, said method comprising administering to said individual an effective amount of at least one compound of formula I:



wherein:

R^1 is $-(C_1-C_7)$ hydrocarbyl or $-(C_2-C_6)$ heteroalkyl;

R^2 is selected from the group consisting of $-H$, and $-(C_1-C_7)$ hydrocarbyl;

wherein R^1 and R^2 may combine to form a carbocyclic or heterocyclic 5- or 6-membered ring;

R^3 is independently selected from the group consisting of $-O(C_1-C_6)$ alkyl, $-OH$, $-O$ -acyl, $-SH$, $-S(C_1-C_3)$ alkyl, $-NH_2$, $-NH(C_1-C_6)$ alkyl, $-N((C_1-C_6)alkyl)_2$, $-NH$ -acyl, $-NO_2$ and halogen;

n is 1, 2 or 3;

R^4 and R^5 are independently selected from the group consisting of $-O(C_1-C_6)$ alkyl, $-OH$, O -acyl, $-SH$, $-S(C_1-C_3)$ alkyl, $-NH_2$, NH -acyl and halogen;

wherein, R^4 and R^5 may combine to form a 5, 6 or 7-membered heterocyclic ring;

or a pharmaceutically-acceptable salt of such a compound.

24. The method according to claim 23, wherein said compound according to formula I is an (*R*)-enantiomer substantially free of the corresponding (*S*)-enantiomer, with respect to the absolute conformation at the 5-position of the benzodiazepine ring.

25. The method according to claim 23 wherein the risk of developing neutropenia is associated with a forthcoming drug therapy.

26. The method according to claim 25 wherein the drug therapy comprises administration of at least one chemotherapeutic agent.

27. The method according to claim 24, wherein the risk of developing neutropenia is associated with a forthcoming exposure to ionizing radiation.

28. The method according to claim 27 wherein the ionizing radiation comprises therapeutic radiation therapy.

29. The method according to claim 27 wherein the ionizing radiation is other than therapeutic radiation therapy.

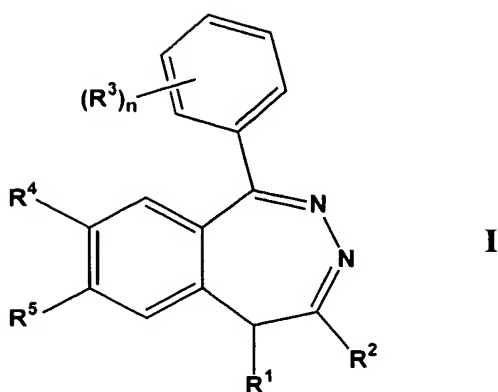
30. The method according to claim 23 wherein the risk of developing neutropenia is associated with immunodeficiency.

31. The method according to claim 30 wherein said immunodeficiency is caused by a cancer.

32. The method according to claim 30 wherein said immunodeficiency is caused by a virus.

33. The method according to claim 32 wherein said virus is human immunodeficiency virus.

34. A method of treating an individual afflicted with neutropenia, comprising administering to said individual an effective amount of a combination of at least one compound of formula I:



wherein:

R^1 is $-(C_1-C_7)$ hydrocarbyl or $-(C_2-C_6)$ heteroalkyl;

R^2 is selected from the group consisting of $-H$, and $-(C_1-C_7)$ hydrocarbyl;

wherein R^1 and R^2 may combine to form a carbocyclic or heterocyclic 5- or 6-membered ring;

R^3 is independently selected from the group consisting of $-O(C_1-C_6)$ alkyl, $-OH$, $-O$ -acyl, $-SH$, $-S(C_1-C_3)$ alkyl, $-NH_2$, $-NH(C_1-C_6)$ alkyl, $-N((C_1-C_6)alkyl)_2$, $-NH$ -acyl, $-NO_2$ and halogen;

n is 1, 2 or 3;

R^4 and R^5 are independently selected from the group consisting of $-O(C_1-C_6)$ alkyl, $-OH$, O -acyl, $-SH$, $-S(C_1-C_3)$ alkyl, $-NH_2$, NH -acyl and halogen;

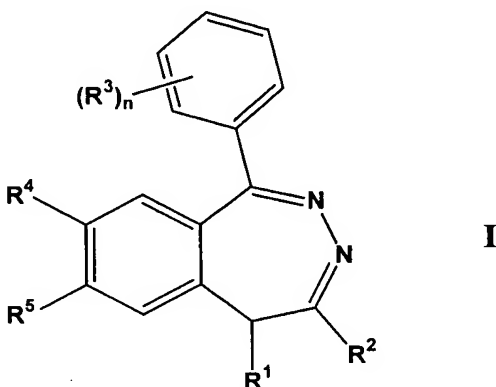
wherein, R^4 and R^5 may combine to form a 5, 6 or 7-membered heterocyclic ring;

or a pharmaceutically-acceptable salt of such a compound; and

one or more additional agents selected from the group consisting of angiogenesis inhibitors; granulocyte colony stimulating factor, granulocyte colony stimulating factor agonists, granulocyte macrophage colony stimulating factor, granulocyte macrophage colony stimulating factor agonists, macrophage colony stimulating factor, macrophage colony stimulating factor agonists, immunomodulators, apoptosis stimulants, chelating agents, interleukin 1-alpha agonists, interleukin 1-beta agonists, interleukin 3 agonists, interferon gamma agonists, stem cell stimulants, tumor necrosis factor agonists, and growth factor agonists.

35. The method according to claim 34 wherein said additional agent is granulocyte colony stimulating factor.

36. A method of preventing neutropenia in an individual who is at risk of developing neutropenia, said method comprising administering to said individual an effective amount of a combination of at least one compound of formula I:



wherein:

R^1 is $-(C_1-C_7)$ hydrocarbyl or $-(C_2-C_6)$ heteroalkyl;

R^2 is selected from the group consisting of $-H$, and $-(C_1-C_7)$ hydrocarbyl;

wherein R^1 and R^2 may combine to form a carbocyclic or heterocyclic 5- or 6-membered ring;

R^3 is independently selected from the group consisting of $-O(C_1-C_6)$ alkyl, $-OH$, $-O$ -acyl, $-SH$, $-S(C_1-C_3)$ alkyl, $-NH_2$, $-NH(C_1-C_6)$ alkyl, $-N((C_1-C_6)$ alkyl) $_2$, $-NH$ -acyl, $-NO_2$ and halogen;

n is 1, 2 or 3;

R^4 and R^5 are independently selected from the group consisting of $-O(C_1-C_6)$ alkyl, $-OH$, O -acyl, $-SH$, $-S(C_1-C_3)$ alkyl, $-NH_2$, NH -acyl and halogen;

wherein, R^4 and R^5 may combine to form a 5, 6 or 7-membered heterocyclic ring;

or a pharmaceutically-acceptable salt of such a compound; and

one or more additional agents selected from the group consisting of angiogenesis inhibitors; granulocyte colony stimulating factor, granulocyte colony stimulating factor agonists, granulocyte macrophage colony stimulating

factor, granulocyte macrophage colony stimulating factor agonists, macrophage colony stimulating factor, macrophage colony stimulating factor agonists, immunomodulators, apoptosis stimulants, chelating agents, interleukin 1-alpha agonists, interleukin 1-beta agonists, interleukin 3 agonists, interferon gamma agonists, stem cell stimulants, tumor necrosis factor agonists, and growth factor agonists.

37. The method according to claim 36 wherein said additional agent is granulocyte colony stimulating factor.